JOUR. DIAB. ASSO. IND. Vol. XXIV, Jan. 1984

ALLERGY TO CONVENTIONAL & MONOCOMPONENT PORCINE & HUMAN INSULINS

MOHAN V.*, CHINNIKRISHNUDU, M.**, BHARANI G.***, SNEHALATHA C.,**** RAMCHANDRAN A.***** and VISWANATHAN M. ******

SUMMARY

While allergy to conventional insulin is quite common, that to M. C. Insulin is comparatively rare. We report here a series of cases of allergy to conventinal insulin and M.C. Insulin. The clinical features, the details of the allergy tests and management of insulin allergy are presented. In general, the allergy was most common with conventional insulins and less common with M.C. Insulin and least common with Human Insulin.

Introduction :

Long term insulin treatment is beset with many clinical problems. Allergy to insulin is one of the prominent among these. Several reports of allergy to conventional insulins have appeared in literature (1-2). Isolated reports on allergy to M.C. Insulin have also appeared in Western literature (3). However, there is paucity of literature on this condition from our country. This paper presents clinical data in patients with allergy to conventional and monocomponent insulin.

Clinical Material :

The clinical material for this study consisted of diabetic patients with Insulin Allergy attending the Diabetes Research Centre and M. V. Hospital for Diabetes, Madras, a large referral Centre for diabetes with an annual registration of over 4,500 diabetics.

Prevalence of Insulin Allergy :

The clinical data of all diabetics attending the Diabetes Research Centre are now computerized. Out of the 4,000 patients entered in the computer file during the year 1982-1983, 400 had been treated with insulin showing that over-all, 10% of patients are treated with insulin. This number includes insulin dependent diabetes (IDDM), insulin requiring NIDDM and others treated with insulin because of pregnancy, infections etc. Out of these 400 patients, there were 24 patients with insulin allergy giving an over all prevalence of 6% of Insulin

* Assistant Director.
** Medical Officer.
*** Fellow in Diabetes.
**** Head Dept. of Biochemisty.
***** Assistant Director.
****** Director.
Diabetes Research Centre
and
M. V. Hospital For Diabetes,
5 Main Road, Royapuram,
Madras-600 013.

Address for correspondence:
Dr. V. Mohan, M.D., Asst. Director.
Diabetes Research Centre and
M. V. Hospital for Diabetes,
5, Main Road, Royapuram,
Madras-600 013.

(Modified Copy Received on 26-10-83)

Allergy among the insulin treated patients. There were 14 males and 10 females. Most patients with allergy were between 40-60 years of age. These figures are consistent with the overall sex and age distribution of diabetics at this Centre. The duration of diabetes for most of the patients was between 1 to 10 years. As many as 8 patients developed allergy within 6 months of treatment with insulin.

Type of Allergy :

The patients were classified based on the type of allergic reaction into :

(a) cutaneous (local),
(b) systemic or
(c) combined allergy.

Cutaneous allergy was defined as being present when allergic symptoms such as itching, erythema, or wheal formation were present at the site of insulin injection or at other sites in the skin. This itself could be of three types(4) :

(a) immediate, if it occured within minutes.
(b) delayed, if it occured after several hours or after 24 hours or
(c) dual, if it was a combination of immediate and delayed types.

Systemic allergy was considered to be present, if urticaria, angioedema, wheeze, bronchospasm, or other respiratory symptoms, gastrointestinal symptoms or polyarthritis etc., were present(4). There were 18 patients with cutaneous allergy, 2 with systemic allergy and 4 patients with both cutaneous and systemic allergy. Of the 18 patients with cutaneous allergy, 10 had immediate, 4 delayed and 4 dual type of allergy.

TYPE OF INSULIN :

While 19 patients were allergic only to conventional insulin, 5 were allergic to M. C. Insulin also and out of them one patient had allergy even to Human Insulin.

Management of Allergy to Conventional Insulin :

In 16 of the 24 patients, the insulin treatment could be stopped and they could be changed over to oral drugs. The other 8 who required Insulin were changed over to Monocomponent Porcine Insulin. Of these eight patients five had a mild form of allergy to M.C. Insulin also. The management of these patients is discussed below.

Allergy to MC Insulin.

Out of the total of 24 patients, 5 patients (20.8%) showed allergic manifestations to M.C. insulin also. Out of these five, four patients showed no allergy to Human Insulin, whereas 1 patient showed mild allergy even to Human Insulin. The clinical details of this latter patient have been published elsewhere (5). The management of allergy to Monocomponent Insulin has also been dealt with elsewhere (6).

Allergy Testing :

In 4 out of these 5 patients, insulin allergy skin tests were carried out to confirm whether the allergy was due to the Insulin itself or to the diluents used in preparation of Insulin. The allergy test kits gifted by the Novo Research Institute, Denmark were used in this trial. The case summaries of these four patients are given below :

Patient No. 1 was a 50 year old lady with diabetes mellitus of 21 years duration. She developed allergy to conventional insulins 7 years after the onset of diabetes, after 2 years of irregular treatment with conventional insulins. As her diabetes could not be controlled with

oral drugs, she was switched on to Actrapid M.C. insulin. After 3 months with Actrapid M.C. Insulin, patient started developing itching all over the body, bronchospasm and sneezing. The allergy skin test showed itching within 10 minutes of the test with Actrapid M.C. Bovine insulin. A wheal also showed up within 10 minutes, gradually increasing in size upto 2 hours. It completely disappeared after a few hours. With Actrapid M.C. Porcine insulin there was very negligible wheal formation which disappeared completely within 20 minutes. No reaction was noticed with Actrapid M.C. Human Insulin and also with the diluting medium.

The next day Human semisynthetic insulin 10 units two times a day was given. No allergic reaction was noted. Even though there was no obvious allergy to Actrapid M.C. Porcine Insulin in this trial, the patient had definite allergy on taking it in the regular doses. She was later desensitized to Actrapid M.C. Insulin and is now able to take Actrapid M.C. Insulin.

Patient No. 2.

The second case was a female patient aged 58 years with diabetes of 10 years duration. For the first 9 years she was treated with Tolbutamide. For the last 1 year, insulin (conventional) had to be given as she developed diabetic ketoacidosis after an infection. She developed insulin allergy after the first few injections itself. Later even M.C. Insulin was found to produce allergic reaction.

On doing allergy skin tests it was seen that after 10 minutes, itching developed around the Actrapid bovine site. After 20 minutes she developed generalized itching. Even though the itching subsided within 24 hours, erythema and slight induration around Actrapid bovine site persisted. This test showed that allergy to Actrapid Bovine was more than to Actrapid Porcine. There was no allergy to human insulin. The patient is now being maintained with glybenclamide and Metformin because of non availability of Human Insulin.

Patient No. 3.

A male patient aged about 61 years with diabetes of 21 years duration, had been treated initially with oral antidiabetic drugs and later had irregular treatment with insulin. He had also treatment for cervical spondylosis in '68 and developed left sided hemiparesis in '79.

Insulin allergy was noticed in '68 when he developed rashes and bullae all over the body accompanied by severe itching soon after the injection of conventional insulin. The rash subsided with antiallergic drugs. Treatment with M.C. Insulin was also found to produce allergic manifestations. When human insulin was tried it was found that the Human Insulin was less allergic compared to Actrapid M.C.

Allergic skin test to Actrapid M.C., Human insulin and the diluents was carried out. There was no erythema either around the diluent injection and very slight erythema around the human insulin injection site. There was a large erythema, 60 mm X 40 mm in size, around the Actrapid M.C. Insulin. A red spot remained at the injection site even after 3 days.

From the above test results, it is obvious that there is no allergy to the diluent while there is definite allergy to Insulin itself. It is apparent that Actrapid

Porcine M.C. Insulin produced greater allergy than Human M.C. Insulin but even human insulin appeared to produce some allergy.

Patient No. 4.

This was a non insulin dependent male patient aged about 47 years with history of diabetes for 8 years. No allergy was noted for the first 5 years during which period, different combinations of plain insulin, PZI and Lente Insulin were given irregularly. Allergy to conventional insulin was noted first in 1979. He started getting oliguria, puffiness of the face, oedema of the body and mild itching by the third day of insulin injection.

During August '80 he was admitted and Actrapid M. C. Insulin was given. No immediate allergic reaction was noted. However he developed delayed allergic symptoms after 24 hours. This patient is now being managed successfully with oral hypoglycemic agents.

Insulin Specific IgE Antibody Estimation :

In collaboration with the Novo Research Institute, Denmark, the serum samples of patients 3 and 4 have been analysed for insulin binding IgG and IgE, antibodies. In patient 3 the IgG was 0.67 mu/ml and IgE 3 u/ml. In patient 4 the IgG was 0.008 mu/ml and IgE was 0.5 u/ml. The insulin binding IgG level of more than 0.05 mu/ml is considered to be positive. The full details of this study have been published elsewhere (7).

It can be seen that the insulin binding IgE which mediates the immediate type of insulin reaction is increased in Case-3. In such cases if desensitisation is carried out successfully, the insulin specific IgE, antibodies can be observed to drop to normal levels which is paralleled by the disappearance of the clinical allergic symptoms.

Discussion :

Insulin allergy is not an uncommon complication of long term insulin treatment (1-3). It often occurs due to presence of impurities of Insulin. One could be allergic to preservatives in the diluting medium (e.g. parabens), the zinc used in the insulin (8), to various additives such as protamine (9) or even to the insulin molecule itself (10). While it is sometimes difficult to determine which of these is producing the allergy in a given case, the authors have been able to reasonably sort out this problem by using the Insulin Allergy test kits. It is now known that there are different types of insulin allergy and that each of these is mediated by a different antibody (11). The immediate allergy is mediated by IgE antibodies whereas delayed allergy is mediated by sensitized lymphocytes.

In earlier days, treatment of Insulin Allergy was limited to use of steroids and antihistamines etc (12). The advent of monocomponent insulin provided an excellent solution to this problem (13, 14, 15). At the Diabetes Research Centre, Madras, M. C. Insulins have been used with very good results in patients with Insulin Allergy (6, 16). However a few patients are found to be allergic even to M. C. Insulin. The use of Human Insulin is useful in some of these cases while in others, Human Insulin is also unsuitable (5). Desensitization to insulin offers yet another solution to the problem. The authors have also used this method with good results (17).

The species of Insulin is also of importance in determining the severity of Insulin Allergy. Transferring the patient

from Bovine to Porcine Insulin is often helpful. In collaboration with the Novo Research Institute, Denmark, we have been able to do Insulin specific IgE, estimations in problem cases of Insulin Allergy. This work has shown that IgE levels are highest in Bovine Insulin treated patients, lower in Porcine Insulin treated group and lowest in those treated with Human Insulin (7).

ACKNOWLEDGEMENT

The authors wish to thank the Novo Research Institute, Denmark and Karen Falholt for the supply of the Insulin Allergy test kits and for the IgG and IgE estimations.

REFERENCES

1. Mattson, J. R., Patterson, R. and Roberts, M.: Insulin therapy in patients with systemic insulin allergy. Ann. Intern. Med. 135: 618-621, 1975.
2. Lenfield, Y.: Insulin allergy. Report of a case with delayed local reaction. Arch. Dermatology. 115: 597-592, 1979.
3. Kumar, D. Insulin allergy. Differences in Binding of Porcine Bovine and Human Insulins with Anti Insulin IgE. Diabetes Care. 5: 104-107, 1981.
4. Elenbass, R. M. and Fooni, P. J.: Am. J. Hosp. Pharm. 33: 1. 491, 1976.
5. Mohan, V., Shyamsundar, R., Ramachandran, A., Viswanathan, M.: Case Report: Allergy to Monocomponent and Human Insulin. J. Assn. Phy. Ind. 31: 721-722, 1983.
6. Mohan, V., Ramachandran, A. and Viswanathan, M.: Monocomponent Insulin in treatment of Diabetes Mellitus. In: Surgical Endocrinology Ed R. Saratchandra, S. Vittal, P. 170-177, 1983.
7. Falholt, K., Hoskan, J. Am., Karamansol, B. G., Snastrank, H., Viswanathan, M. and Heding, L. G.: Diabetes Care. 6: 61-65, 1983.
8. Feinglos, M. N., Jegarothy, B. V.: Insulin Allergy due to Zinc. Lancet. 122-124, 1979
9. Shore, R. N., Shelley, W. B. and Kyle, G. C.: Arch. Derm. 1111, 94, 1975.
10. Federlin, K. In: Insulin Part 2. Handbook of Experimental Pharmacology. Vol. XII. Edited by A. Hasselblatt, F. W. Bnuchhausen. Berlin. P-569, 1975.
11. Andreani, D., Menzinger, G., Di Mario, U., Scarsetta, M. and Jancoli, M.: Clinical use of Monocomponent Insulin preparations. XIVth International Congress of Therapeutics. Montpeller (France). L' Expansion Scientifique Francaise, Publisher, P-9, 1977.
12. Lamkin, N., Libermam, P., Hashimoto, K., Morohashi, M. and Sullwan, P.: Allergic Reactions to Insulin. Allergy Grand Rounds. Vol. 38:1 Part-2, 213-223, 1978.
13. Tuescher, A.: The place of Monocomponent Insulin in the therapy of Diabetes Mellitus. Schewerg Med. Wschr. 105, 485-494, 1975.
14. Federlin, K., Velcosthy, H. G. and Masa, E.: Clinical aspects of immunity to Insulin. In: Basic and Clinical Aspects of Imunity to Insulins. Ed. Keek, Drb, Walker, Dc Griyter & Co., Berlin. P. 203-217, 1981.
15. Krelines, K.: The use of various Insulins in Insulin Allergy. Ann. Intern. Med. 116: 167-171, 1965.
16. Ramachandran, A., Mohan, V., Viswanathan, M., Snehalatha, C., Shyamsundar, R.: Monocomponent insulin in management of diabetes. A follow-up study. J. Diab. Assn. Ind. 22: 60-63, 1982.
17. Mohan, V., Viswanathan, M., Chinnikrishnudu, M.: J. Assn. Phy. Ind. In Press.